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Voluma: A Systematic Review of Clinical Experience

Derek Ho BS[a] and Jared Jagdeo MD MS[a,b,c]
[a]Dermatology Service, Sacramento VA Medical Center, Mather, CA
[b]Department of Dermatology, University of California Davis, Sacramento, CA
[c]Department of Dermatology, State University of New York Downstate Medical Center, Brooklyn, NY

ABSTRACT

Background: Dermal fillers are important for facial aesthetic enhancement as patients are favoring non-surgical procedures with minimal recovery time. Voluma is a volumizing hyaluronic acid filler, 20 mg/ml HA dermal filler, which was FDA-approved in 2013 as the first dermal filler for treatment of age-related volume loss in the midface.

Objective: We sought to systematically review clinical studies and expert opinions of this 20 mg/ml HA dermal filler and to provide evidence-based recommendations and expert opinions.

Methods and Materials: A search of the computerized bibliographic databases Medline, Embase, Embal, Biosis, SciSearch, Pascal, HCAPlus, IPA, and Dissertation Abstracts was performed on August 18th 2014.

Results: Thirteen articles met inclusion and were included in our review: clinical trials with this 20 mg/ml HA dermal filler (10) and expert opinions and questionnaire survey studies of experts (3). This 20 mg/ml HA dermal filler has shown consistent, favorable results for treatment of age-related facial volume loss, aesthetic enhancement, and HIV facial lipoatrophy.

Conclusion: HA fillers are safe and effective with minimal recovery time and complications. Future studies with longer follow-up period and use of this 20 mg/ml HA dermal filler on areas other than midface may provide additional efficacy and safety outcomes.

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INTRODUCTION

Dermal fillers are increasing in popularity as new filling products are introduced to the market. Fillers allow for non-surgical reduction of facial wrinkles and restoration of facial volume. The FDA classifies these dermal fillers as "devices." The main ingredient of fillers currently available on the market include hyaluronic acid (HA), poly-L-lactic acid (PLLA), poly[methyl methacrylate] (PMMA), and calcium hydroxylapatite (CaHA). Through research, physicians and scientists have a better understanding of the pathogenesis of skin aging, and treatments for age-related skin changes have moved from a two-dimensional approach with rhytid correction and facial musculature relaxation to a three-dimensional approach with facial volumization.[1-3] In 2013, the American Society for Dermatologic Surgery (ASDS) reported 995,000 soft-tissue filler procedures in the United States, an increase of 8.6% from 2012.[4]

Voluma is a volumizing hyaluronic acid filler, 20 mg/ml HA dermal filler (Juvéderm Voluma®, Allergan Inc., Irvine, CA), which was FDA-approved in 2013 as the first filler approved in the U.S. to improve age-related volume loss in the midface. We sought to systematically review clinical studies and expert opinions of this 20 mg/ml HA dermal filler and to provide evidence-based recommendations and expert opinions.

METHODS

Literature Search Strategy

Our goal was to analyze all clinical trials conducted with this 20 mg/ml HA filler. A search of the computerized bibliographic databases Medline, Embase, Embal, Biosis, SciSearch, Pascal, HCAPlus, IPA, and Dissertation Abstracts was performed on August 18th 2014. The key term used was "Voluma." The bibliographies of all relevant articles were checked for additional articles that could not be identified in our search.

Inclusion and Exclusion Criteria

The relevant articles that met the following criteria were selected for inclusion: original clinical research studies and expert's opinion publications that investigated or discussed the use of this 20 mg/ml HA filler. Exclusion criteria included: posters/abstracts, non-patient based studies, English literature review articles, and non-English articles.

Study Selection and Data Extraction

Titles and abstracts from the electronic search were screened, and full-text articles that met the selection criteria were obtained. Information on study design, sample size, treatment regimen, follow-up periods, study outcomes, and adverse events were extracted. Two reviewers (D.H. and J.J.) independently extracted data from eligible studies and any differences were resolved through consensus.

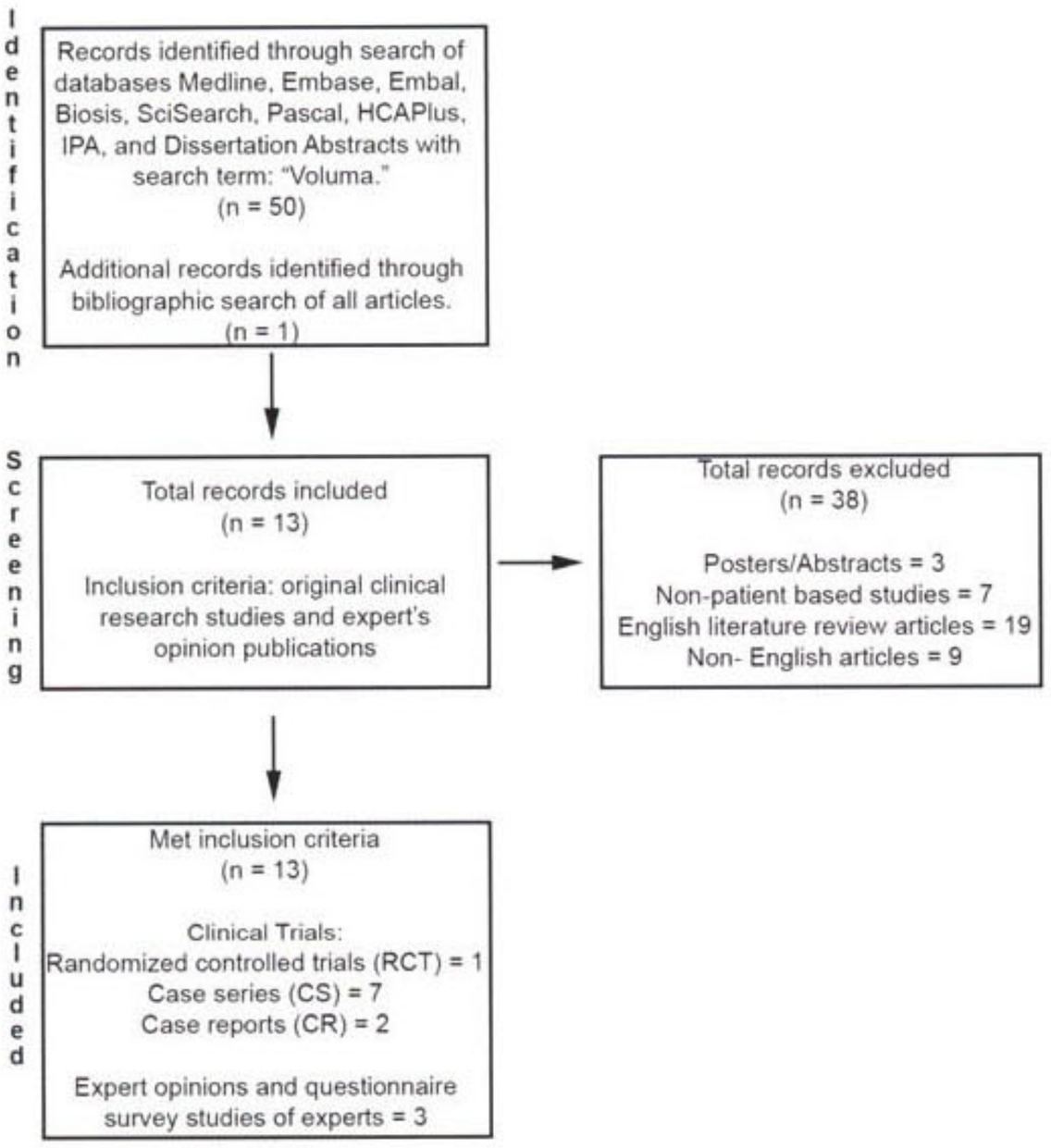
RESULTS

There were a total of 50 articles that populated in our search. Articles that were not identified from the original search but from manual identification from bibliographies were included (1). Excluded articles include: posters/abstracts (3), non-patient

based studies (7), English literature review articles (19), and non-English articles (9).

After screening of titles, abstracts, and full-text articles, 13 of these articles were suitable in our review (Figure 1). The articles consist of: clinical trials with this 20 mg/ml HA dermal filler (10) and expert opinions and questionnaire survey studies of experts (3). Articles were assigned a level of evidence (LOE) and afterward graded according to the Oxford Center for Evidence-based Medicine Levels of Evidence Grades of Recommendation (GOR)[5] criteria (Tables 1 and 2). Detailed information describing each unique record is shown in Table 3.

FIGURE 1. Schematic of the search strategy listing the number of articles matching inclusion or exclusion criteria. Adapted from Moher et al.[21]


Identification
Records identified through search of databases Medline, Embase, Embal, Biosis, SciSearch, Pascal, HCAPlus, IPA, and Dissertation Abstracts with search term: "Voluma."
(n = 50)
Additional records identified through bibliographic search of all articles.
(n = 1)
Screening
Total records included
(n = 13)
Inclusion criteria: original clinical research studies and expert's opinion publications
Total records excluded
(n = 38)
Posters/Abstracts = 3
Non-patient based studies = 7
English literature review articles = 19
Non- English articles = 9
Included
Met inclusion criteria
(n = 13)
Clinical Trials:
Randomized controlled trials (RCT) = 1
Case series (CS) = 7
Case reports (CR) = 2
Expert opinions and questionnaire survey studies of experts = 3

Clinical Studies and Expert Opinions of 20 mg/ml HA Dermal Filler

Aging-related Facial Volume Loss

A prospective, randomized, single-blind, multicentered, controlled clinical trial in U.S. studied the efficacy and safety of this 20 mg/ml HA dermal filler on 282 patients with age-related facial volume loss[6] (LOE 1b). MidFace Volume Deficit Scale (MFVDS) scores facial volume loss from none (0) to severe (5) (MSVDS; Data on file, Allergan, 2012). 3-D images were taken each visit to determine facial volume changes. Results showed that at 6 months, 85.6% of patients in the treatment group improved by 1+ point on the MFVDS (responders) and had a significant difference compared to control group. Global Aesthetic Improvement Scale (GAIS) showed 82.2% of physicians and 92.8% of patients rated the volume changes as "improved" or "much improved" by 6 months. 3-D images showed a mean midface volume increase of 6.8 ml (treatment group) versus 0.8 ml (control group). Adverse events were mild and transient that included injection site lumps or bumps, induration, swelling, and pain. This is one of the most significant studies to date with results from randomized patients, and results showed that this 20 mg/ml HA dermal filler is robust with 44.6% of patients rated as "responders" at 2 years.

TABLE 1.

Level of Evidence (LOE)
1a. Systematic review of RCTs
1b. Individual RCT
2a. Systematic review of cohort studies
2b. Individual cohort study (including low-quality RCT)
3a. Systematic review of case-control studies
3b. Individual case-control study
4b. Case series
5. Case reports, expert opinion

RCT, Randomized controlled trial.
Data from Oxford Center for Evidence-based Medicine Levels of Evidence.[21]

In 2008, a case series in France studied the efficacy and safety of this 20 mg/ml HA dermal filler on 102 subjects with age-related volume loss[7] (LOE 4). GAIS showed that at 1 month and 6-18 months post-treatment, 98% and 82% of patients, respectively, were either "very much improved" or "much improved." A majority of subjects (98%) rated their treatments as "very good" or "good," and had a higher quality-of-life (QOL) post-treatment. There were 9 transient adverse events including swelling, hematoma, overcorrection, and hypersensitivity.

A European case series studied the efficacy and safety of this 20 mg/ml HA dermal filler on 70 subjects with age-related facial volume loss[8] (LOE 4). 29% of subjects post-treatment, compared to 78% of subjects pre-treatment, had a medium degree of volume loss. GAIS showed

TABLE 2.

Grades of Recommendation (GOR)
A. Studies with consistent LOE 1a and/or 1b
B. Studies with consistent LOE 2a, 2b, 3a, or 3b; or extrapolations from studies with LOE 1a or 1b
C. Studies with LOE 4 or extrapolations from studies with LOE 2a, 2b, 3a, or 3b
D. Studies with LOE 5 or troubling inconsistent or inconclusive studies of any level

LOE, Level of evidence.
Data from Oxford Center for Evidence-based Medicine Levels of Evidence.[21]

TABLE 3.

Published Clinical Experiences With this 20 mg/ml HA Dermal Filler (Juvéderm Voluma®, Allergan Inc., Irvine, CA)						
	Author	**LOE**	**Study Type**	**Number of patients**	**Results**	**Adverse Events**
	Age-related Facial Volume Loss [Grade of Recommendation (GOR): A]					
1.	Jones *et al.* [6], 2013	1b	Prospective, randomized, single-blind, multicentered	282	**GAIS** "Improved" or "much improved" Physician rated – **82.2%** Subjects rated – **92.8%**	n = 15 Injection site mass (18.9%), induration (14.1%), swelling (7.0%), pain (5.9%)
2.	Raspaldo *et al.* [7], 2008	4	Case Series	102	**GAIS** "Very much improved or much improved" 1 month post-treatment: **98%** 6-18 months post treatment: **82%**	n = 9 Swelling, hematoma, overcorrection and hypersensitivity (Longest event resolved in 21 days)
3.	Hoffmann *et al.* [8], 2009	4	Case Series	70	**GAIS** "Very much improved or much improved" Visit 2 follow-up: **88%**	n = 24 Bruising, pain and swelling (Mean duration 5.5 days)
4.	Fischer *et al.* [9], 2010	4	Case Series	84	Investigators Rated this 20 mg/ml HA dermal filler as "very much better, much better or better" than previously used Restylane® in **69.1%** of patients Expressed preference for this 20 mg/ml dermal HA filler over Restylane® in **71.4%** of patients	n = 7 Bruising and swelling (Mean duration 6.57 days)
5.	Callan *et al.* [10], 2013	4	Case Series	103	GAIS 8 weeks post-treatment: **100%** 52 weeks post-treatment: **88.2%** 78 weeks post-treatment: **78.1%**, (total of 82 subjects attended this visit) 102 weeks post-treatment: **91.1%**, (total of 72 subjects attended this visit, but only 45 were included in the analysis because they did not require retreatment at week 78)	n = 77 Bruising and swelling (64), pain/ tenderness, and erythema.
6.	Philipp-Dormston *et al.* [11], 2014	4	Case Series	115	MFVDS Scored moderate, significant or severe Baseline **72.2%** Immediately post-treatment **12.2%** 21 days post-treatment **8.9%** Scored none, minimal and mild Baseline **27.8%** Immediately post-treatment **87.8%** 21 days post-treatment **91.1%**	n = 5 Edema, swelling, hematoma and pain at injection site.
7.	Carruthers *et al.* [12], 2010	5	Expert"s opinion	n/a	This 20 mg/ml HA dermal filler for midface volume replacement with satisfying outcomes. Mentioned use of this 20 mg/ml HA dermal filler near periocular region.	None.
8.	Raspaldo *et al.* [14], 2011	5	Expert"s opinion	n/a	This 20 mg/ml HA dermal filler creates volumization in deep tissues and complement well with Juvederm® Ultra and BoNTA®	None.

	Author	LOE	Study Type	Number of patients	Results	Adverse Events
	Aesthetic Enhancement [Grade of Recommendation (GOR): C]					
1.	Bae *et al.* [15], 2013	4	Case Series	320	**GAIS** "Much improved" or "very much improved" Physician rated – **97.2%** Subjects rated – **94.0%**	n = 96 Mild edema (82%), bruising (18%)
2.	Wong *et al.* [16], 2011	5	Case report	1	This 20 mg/ml HA dermal fllller used for midface augmentation highlighted contours of the face with satisfying results.	None
3.	Gilbert and Calvisi [17], 2014	5	Case report	1 with this 20 mg/ml HA dermal filler (7 total)	Calvisi commented on this 20 mg/ml HA dermal filler being effective for up to 15 months.	None
4.	Lee *et al.* [18], 2014	5	Expert"s opinion	n/a	This 20 mg/ml HA dermal filler has high visco-elasticity and longevity, suitable for nasolabial folds, filler rhinoplasty, and forehead augmentation.	None
	HIV- associated Facial Lipoatrophy [Grade of Recommendation (GOR): C]					
1.	Bechara *et al.* [19], 2008	4	Case Series	21	**GAIS** "Much improved or better" 3 months post-treatment: **90.5%** 6, 9 months post-treatment: **100%** 12 months post-treatment: **85.7%**	Mild erythema (38.1%), swelling (19%), discrete bruising (19%)

LOE, Level of evidence. *GOR*, Grades of Recommendation. *GAIS*, Global Aesthetic Improvement Scale. *MFVDS*, MidFace Volume Deficit Scale

88% of subjects were rated as "very much improved" or "much improved." Patient satisfaction surveys indicated 92% of subjects would return for treatment, and 98% of subjects would recommend treatment to their friends. 24 subjects experienced temporary adverse events including bruising, pain, and swelling.

A case series in Germany demonstrated efficacy and safety outcome with this 20 mg/ml HA dermal filler in 84 subjects who previously used Restylane Sub-Q™ (Restylane)[9] (LOE 4). Investigators rated this 20 mg/ml HA dermal filler as "very much better, much better or better" than their previous experience with Restylane in 69.1% of subjects. Over 70% of subjects rated their satisfactions as "somewhat or significantly better" with current treatment when compared to Restylane. A majority (97%) of subjects were "happy or delighted" with this 20 mg/ml HA dermal filler, and 96.4% of them would recommend it to their friends. There were seven transient adverse events including bruising and swelling.

An Australian case series highlighted the efficacy and safety of this 20 mg/ml HA dermal filler for age-related volume loss in 103 subjects[10] (LOE 4). MFVDS responders included 96% of subjects at week 8, 88.2% at week 52, and 81.5% at week 78. Out of 72 subjects who completed the study at week 104, 45 of them needed no retreatment at week 78, and were included in the final analysis at week 108 with 95.6% subjects as responders. GAIS showed physicians rated 100% responders at week 8, 88.2% at week 52, 78.1% at week 78, and 91.1% at week 102. There were 91.6% of subjects who rated themselves as "satisfied or very satisfied" with this treatment, and 97.2% of subjects would recommend treatment to others. There were 77 transient adverse events including injection site bruising and swelling (64 cases), pain/tenderness, and erythema.

A different case series investigated the efficacy of this 20 mg/ml HA dermal filler on age-related facial volume loss in 115 subjects[11] (LOE 4). Immediately after treatment, 95.6% of subjects were "delighted or happy" and by day 21, satisfaction maintained in 93.8% of subjects. MFVDS showed that 72.2% of subjects was "moderate, significant or severe" pre-treatment and significantly decreased to 12.2% immediately post-treatment, and 8.9% by day 21. Over 93% of investigators considered their treatment outcomes as "much improved or very much improved" both immediately after treatment and by day 21.

An expert's opinion article highlighted anecdotal experiences with this 20 mg/ml HA dermal filler[12] (LOE 5). The authors commented on their positive outcomes they had with patients using this 20 mg/ml HA dermal filler for volume replacement in the midface, and suggested the use of this 20 mg/ml HA dermal filler for treatment of aging effects near the periocular region. Previously, there was one other published report that supported the use of HA fillers to increase upper eyelid fullness in aging eyes.[13]

> "This study combined with studies on age-related volume loss indicates this 20 mg/ml HA dermal filler is an effective facial volumizer in young and old patients."

A different expert's opinion study asked a panel of 18 experts on their uses of Juvéderm Voluma®, Juvéderm Ultra® (Ultra), and Botox® (Botulinum Toxin A, Allergan Inc.) (LOE 5).[14] Results showed that this 20 mg/ml HA dermal filler was primarily used in the mid-face, palpebral jugal groove, and nasolabial folds. The panel concluded that the goal for correction of age-related volume loss is not only to reduce rhytides and fill nasolabial folds, but also to create a smooth contoured mid-face with volumization.

Conclusion

Grade of Recommendation: A for treatment of age-related facial volume loss (1 study LOE 1b, 5 case series LOE 4, 2 expert's opinion LOE 5). We believe this 20 mg/ml HA dermal filler represents an effective therapeutic option for volumization of age-related midface volume loss, and we envision it may also represent a potential therapeutic for treatment of aesthetic enhancement and HIV-associated facial lipoatrophy.

Aesthetic Enhancement

A case series in Korea investigated the efficacy and safety of this 20 mg/ml HA dermal filler on 320 young, healthy subjects for aesthetic enhancements[15] (LOE 4). The goal was to improve from a generally flatter and wider face common in Asians to a more anteriorly projected and narrower face more commonly seen in Caucasians. GAIS showed physicians and subjects rated 97.2% and 94.0% of subjects, respectively, as "much improved" or "very much improved." There were 96 transient adverse events, which included mild edema (82%) and bruising (18%).

One case report reviewed the authors' experiences with this 20 mg/ml HA dermal filler for volume augmentation in the mid-face[16] (LOE 5). The authors reviewed a patient who had benign masseteric hypertrophy and wanted to change her prominent rounded lower face. Results showed that midface augmentation highlighted contours of the face, and the authors found that this 20 mg/ml HA dermal filler, in combination with other products, was particularly effective for helping patients with plump faces or cheeks that lack definition.

An observational study assessed different approaches to midface, lip and perioral volume restoration between United States and Italy[17] (LOE 5). One Italian patient had midface volume loss after rapid weight loss from a recent pregnancy. She received 1 mL of this 20 mg/ml HA dermal filler per side for her midface volumization treatment and experienced no adverse events. The authors stated their choice for this 20 mg/ml HA dermal filler was due to its durability in comparison to other HA fillers. They noted that this 20 mg/ml HA dermal filler was effective for up to 15 months post-injection, and is a safe and effective product for treatment of midface volume loss.

One study evaluated 10 Korean dermatologists' preferences for their filler selections used in nasolabial folds, tear troughs, filler rhinoplasty, and forehead augmentation.[18] This 20 mg/ml HA dermal filler was the preferred filler for forehead augmentation. For filler rhinoplasty and nasolabial folds, this 20 mg/ml HA dermal filler, together with Radiesse®, was the top 2 choices. These results demonstrated that this 20 mg/ml HA dermal filler placed very high in categories requiring high visco-elasticity and longevity, and is an excellent option for facial volumization.

Conclusion

Grade of Recommendation: C for aesthetic enhancement (1 case series LOE 4, 2 case reports LOE 5, 1 expert's opinion LOE 5). We believe that 20 mg/ml HA dermal filler is an effective option for facial aesthetic enhancement in young adults. We anticipate that this dermal filler will become increasingly used for aesthetic enhancement in young adults and additional data, preferably from RCTs, is needed to increase the GOR for aesthetic enhancement.

HIV-associated Facial Lipoatrophy

A prospective, open-label, single centered study in Germany investigated the efficacy and safety of this 20 mg/ml HA dermal filler on 21 patients with HIV-associated facial lipoatrophy[19] (LOE 4). At 3 months, 6 and 9 months, and 12 months, GAIS showed "much improved or better" for 90.5%, 100% and 85.7% of patients, respectively. Dermatology Life Quality Index (DLQI) showed a significant reduction of impairment from baseline to end of 12 months, and 95.2% of patients felt the treatment was "beneficial." There were transient adverse reactions including mild erythema (38.1%), swelling (19%), and discrete bruising (19%).

Conclusion

Grade of Recommendation: C for treatment of HIV-associated facial lipoatrophy (1 study LOE 4). We believe this 20 mg/ml HA

dermal filler is an effective therapeutic option for correction of HIV-associated facial lipoatrophy, and additional randomized controlled trials may elucidate the long-term efficacy and safety outcomes of this dermal injectable for treatment of HIV facial lipoatrophy.

DISCUSSION

Biophysical studies of this 20 mg/ml HA dermal filler indicate that this filler has intermediate elasticity and viscosity, which may be an ideal balance between a robust filler with minimal gel migration and high volumization properties, and a viscous, smooth-flowing filler for easy molding.[20] This 20 mg/ml HA dermal filler has shown consistent, favorable results for treatment of age-related facial volume loss in several clinical trials. Currently, there is one LOE 1b RCT, five LOE 4 case series, and two LOE 5 expert's opinion. Subjects with age-related volume loss responded well to treatment. According to physician-rated GAIS, nearly all clinical trials showed >90% of subjects as "improved" or "much improved" at the first visit post-treatment. One touchup treatment was sometimes needed at one month, and results were long-lasting with up to 24 months in one study.

We found this 20 mg/ml HA dermal filler was generally safe with mild, transient adverse events for treatment of age-related facial volume loss. Subjects may experience common temporary adverse reactions including injection site bruising, pain, and swelling. Across all clinical studies, the majority of the subjects felt that this treatment was beneficial, would try this 20 mg/ml HA dermal filler again and would recommend this 20 mg/ml HA dermal filler to friends.

One LOE 4 case series, two LOE 5 case reports and one LOE 5 expert's opinion explored the effects of this 20 mg/ml HA dermal filler as an aesthetic enhancement on young women (mean age 29.4), and over 94% of physicians and subjects rated the outcome as "much improved" or "very much improved." Most adverse events were mild and were well tolerated by subjects. Future studies using this 20 mg/ml HA dermal filler in younger population will be beneficial. This study combined with studies on age-related volume loss indicates this 20 mg/ml HA dermal filler is an effective facial volumizer in young and old patients.

One LOE 4 case series studied the effects of this 20 mg/ml HA dermal filler on patients with HIV-associated facial lipoatrophy. At 12 months, over 85% of patients were rated as "much improved or better." Over 90% of patients found this 20 mg/ml HA dermal filler beneficial and would make recommendations to their friends. Common transient adverse events occurred with no permanent effects. Additional studies are needed to confirm the efficacy of this 20 mg/ml HA dermal filler in patients with HIV facial lipoatrophy. Our research group is currently conducting a clinical trial in the U.S. to study the efficacy and safety of this 20 mg/ml HA dermal filler for treatment of HIV facial lipoatrophy (ClinicalTrials.gov, NCT02342223). We envision treatment of HIV facial lipoatrophy as a potential new indication for this filler because HA fillers may have fewer potential side effects compared to current fillers to treat HIV facial lipoatrophy and are reversible with hyaluronidase.

CONCLUSION

There has been a rapid expansion of facial filler products in the market within the past 10 years. People who wish to look younger and minimize the signs of aging are seeking noninvasive techniques rather than conventional surgery. HA fillers are safe and effective with minimal recovery time and complications. HA fillers are temporary and patients may need retreatment one to two years post- initial treatment. This 20 mg/ml HA dermal filler may help alleviate this problem, and the results to date from available clinical studies showed results lasting up to 24 months. Future studies will benefit from a longer follow-up period and the use of this 20 mg/ml HA dermal filler on areas other than midface to establish a more comprehensive efficacy profile. It will also be interesting to investigate if this 20 mg/ml HA dermal filler is a good adjunct with other dermal fillers as it is becoming more common to use more than one type of dermal fillers for aesthetic enhancement. We look forward to investigating other uses of this 20 mg/ml HA dermal filler, especially in patients with HIV facial lipoatrophy.

DISCLOSURES

Jared Jagdeo, MD, MS is currently conducting an investigator-initiated study on Voluma treatment of HIV facial lipoatrophy (grant, Allergan, Inc.) and on the facial aesthetics advisory board (honoraria, Allergan, Inc.).

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AUTHOR CORRESPONDENCE

Jared Jagdeo MD MS
E-mail:..... jrjagdeo@gmail.com